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Clinical significance of ventilation/perfusion scans in collagen disease patients

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The purpose of this study was to detect disturbances in pulmonary circulation in collagen disease patients by means of a non-invasive technique. ***Methods:*** Ventilation/perfusion scans with ^{133}Xe gas and ^{99m}Tc-macroaggregated albumin (MAA) were performed in 109 patients with various collagen diseases. Functional images of V, Vol, Q and V/Q ratio were obtained at total lung capacity. Wash-out time was calculated from the wash-out curve. Whole body scans were performed in 65 patients to evaluate intra-pulmonary shunts. ***Results:*** Increased V/Q areas were observed in 74 patients (67.9%), suggesting some impairment of pulmonary perfusion. Decreased perfusion, probably due to vasculitis or intravascular microcoagulation, was observed often, even in patients without pulmonary fibrosis. Shunt ratios over 10% were observed in 8 of the 65 patients (12.3%), indicating formation of PA-PV shunts secondary to peripheral vascular impairment. Wash-out time was prolonged in 37 patients (33.9%), shortened in 18 (16.5%), and within the normal range in 54 (49.6%). The prolonged and normal wash-out times in the patients with pulmonary fibrosis may represent obstructive changes in the small airways superimposed on the fibrosis. ***Conclusion:*** Ventilation/perfusion scans are a very useful tool for evaluating collagen lung diseases, and they might contribute to treatment decisions for the patients.

Key words: ventilation/perfusion, collagen disease, pulmonary fibrosis, pulmonary hypertension, pulmonary shunt

INTRODUCTION

PATIENTS with collagen diseases often have a variety of lung disorders, ultimately leading to pulmonary fibrosis and/or pulmonary hypertension,[1] and pulmonary hypertension has been considered one of the most important factors affecting patients' long-term survival.[2] In our clinical experience, patients with collagen disease occasionally show various grades of hypoxemia and/or decreased pulmonary diffusion capacity (D_{LCO}), even in the absence of evidence of pulmonary fibrosis or alveolitis on chest X-rays or CT scans. In spite of physicians' interest in the pulmonary complications of collagen diseases, there have been few reports in the literature of studies evaluating collagen diseases by ventilation/perfusion scintigraphy. The authors expected ventilation/perfusion scintigraphy might have the potential to disclose disturbances in pulmonary circulation secondary to vasculitis, intimal hyperplasia, or intravascular microcoagulation in patients with collagen lung diseases, even in the early stage. The purpose of this study is to evaluate pulmonary circulation in collagen disease patients by means of ventilation/perfusion scan, which is non-invasive and easily performed.

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MATERIALS AND METHODS

Patients:

One hundred and nine patients with various collagen diseases, with or without pulmonary fibrosis, were examined by ventilation/perfusion scintigraphy between

Table 1 Number of collagen disease patients with increased V/Q

Diseases		Without fibrosis		With fibrosis
		APS (−)*	APS (+)	APS (−)#
SLE	34	12/15	9/15	4/4
RA	22	8/9	1/1	9/12
PSS	20	3/4	0	10/16
DM & PM	11	4/6	0	2/5
MCTD	9	4/8	0	1/1
SjS	8	3/3	1/1	3/4
Raynaud	3	2/3	0	0
PN	1	0/1	0	0
Behçet	1	1/1	0	0
Total No.	109	34/50 (68.0%)	11/17 (64.7%)	29/42 (69.0%)
% of patients with increased V/Q in total		31.2%	10.1%	26.6%

* APS: Antiphospholipid antibody syndrome.
# None of the patients with APS have fibrosis in this series.

February 1995 and October 1997. The patients were 19 males and 90 females who ranged in age from 21 to 81 years (mean: 50.8 years). The collagen diseases included 34 cases of systemic lupus erythematosus (SLE), 22 cases of rheumatoid arthritis (RA), 20 cases of progressive systemic sclerosis (PSS), 11 cases of dermatomyositis (DM) or polymyositis (PM), 9 cases of mixed connective tissue disease (MCTD), 8 cases of Sjögren's syndrome (SjS), 3 cases of Raynaud's syndrome, one case of polyarteritis nodosa (PN) and one case of Behçet's disease (Table 1). Diagnosis was made by specialists according to diagnostic criteria. Anticardiolipin antibody, one of the antiphospholipid antibodies, was examined in all patients followed by measurement of lupus anticoagulant in the positive cases with antibody. Seventeen of the 109 patients (15.6%) showed signs of antiphospholipid antidody syndrome (APS), and 15 of them suffered from SLE.

Forty-two of these patients (38.5%) had already had various grades of pulmonary fibrosis at the time of examination. Pulmonary fibrosis was diagnosed with high resolution CT (HRCT) within 2 weeks before or after ventilation/perfusion scan. Only 3 patients received transbronchial biopsy, and cardiac catheterization with pulmonary arteriography was performed in only 2 patients who had mild pulmonary hypertension in this series. Thermography was performed in 12 patients who had Raynaud's phenomenon. Pulmonary function tests were carried out in all patients before the V/Q study.

None of the patients had any history of smoking, occupational lung diseases, bronchial asthma or pulmonary emphysema except for collagen diseases.

Ventilation study:
A mixture of 370 MBq of ^{133}Xe gas and oxygen was placed in the ^{133}Xe delivery system (^{133}Xe Gas Control System, Anzai, Japan) connected to a mask adjusted to provide an airtight seal, while the patient lay in the supine position on the table.

Immediately after the ventilator was turned on, the patient was asked to inhale the gas mixture as deeply as possible and hold his or her breath at the total lung capacity (TLC) point for 15 seconds to obtain the regional ventilation image (V).

The patient then rebreathed the gas mixture in the delivery system for 5 minutes. After reaching an equilibrium gas concentration in the lung, the patient again inhaled the gas mixture to TLC, and held one's breath for 15 seconds to obtain the lung volume image (Vol), i.e. equilibrium wash-in image. Finally, the wash-out images were obtained for 5 minutes or more to record a wash-out curve. Data acquisition was 5 sec/frame in a 64 × 64 matrix by means of an LFOV gamma camera (GCA-90B, Toshiba Medical systems, Japan) with a low-energy, high-sensitivity, parallel-hole collimator.

Perfusion study:
Immediately after the ventilation study, the patient was given an intravenous bolus injection of 185 MBq of ^{99m}Tc-macroaggregated albumin (MAA) in the same position. Data acquisition in the dynamic study was 1 sec/frame for 30–40 sec in a 64 × 64 matrix. Soon after the lung activity reached a plateau, breath-holding for 15 seconds at TLC was performed to obtain the perfusion image (Q). After the dynamic study, planar images in 6 directions (anterior, posterior, bilateral, right posterior oblique and left posterior oblique views) were taken by acquiring 1000 k counts/image in a 512 × 512 matrix.

Whole body scan:
Whole body scanning was performed to evaluate PA-PV shunts in 65 patients. After the perfusion study and about 30 minutes after injection of MAA, the whole body image was obtained with a dual-head camera (GCA-90A-E2, Toshiba Medical Systems, Japan) at a scan speed of 30 cm/min. The shunt ratios were calculated according to the following formula.

$$\text{Shunt ratio (\%)} = \frac{(\text{whole body count} - \text{BG}) - (\text{total lung count} - \text{BG})}{(\text{whole body count} - \text{BG})} \times 100$$

BG (background): Counts 12 pixels beside patient's thigh converted for same area of ROI.

Because physiological shunts are generally observed at a ratio of 3–6%,[3] we used shunt ratios greater than 10% as the abnormal range. Ratios between 7% and 10% were considered equivocal.

Data analysis:
V/Q images were calculated from the corresponding V and Q images with a data processor (GMS-55U; Toshiba

Medical Systems, Japan).

In consideration of the difference in photon energy between ^{99m}Tc and ^{133}Xe, V/Q images of 10 patients with lung cancer, who had a normal lung on the opposite side, were investigated as a control study. The mean V/Q ratio of the normal lungs of these patients was calculated to be 0.98 ± 0.11. In the supine position, there is no evident differences in the V/Q ratio between the upper and lower lung fields. The authors determined the cut-off value of the increased V/Q ratio to be more than 1.25.

Wash-out time (mean transit time) and functional images were calculated from the wash-out curve. Wash-out times between 59 and 40 sec were considered normal. The standard value in our hospital was obtained from 10 normal volunteers of which the average age was 39.4 years.

Table 2 Location of increased V/Q areas in the lung

Diseases		Upper lobe	Lower lobe	Apex & base	Diffuse but inhomogeneous
SLE	24	5 (1)	18 (5)	0	1 (1)
RA	17	0	14 (4)	2	1
PSS	14	7 (2)	5 (1)	1	1
DM & PM	5	1	4 (1)	0	0
MCTD	4	0	2 (1)	1	1
SjS	6	1	4 (2)	1	0
Raynaud	2	0	2	0	0
PN	1	0	1	0	0
Behçet	1	0	1 (1)	0	0
Total No.	74	14 (3)	51 (15)	5	4 (1)
% 100		= 18.9%	= 68.9%	= 6.8%	= 5.4%

( ): unilateral distribution

RESULTS

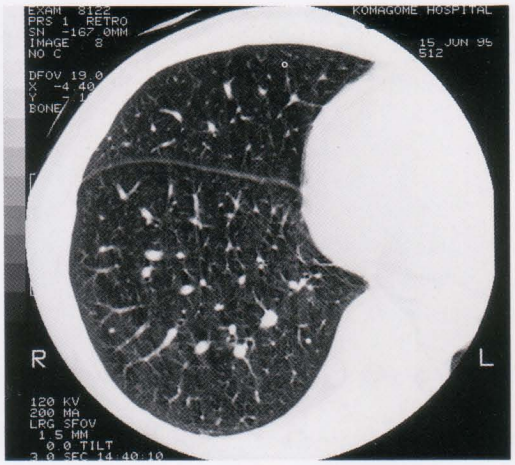
Increased V/Q areas were detected in 74 patients (67.9%), suggesting some impairment of pulmonary perfusion. Eleven of 17 patients with antiphospholipid antibody syndrome (APS) had an increased V/Q ratio. Fifty patients in our series (45.9%) revealed no pulmonary evidence of collagen lung disease, but 34/50 (68.0%) showed increased V/Q areas in the examination (Table 1). None of the patients in this series had a decreased V/Q ratio. No antiphospholipid antibody was detected in the patients with pulmonary fibrosis in this series.

Table 2 summarizes the locations of the increased V/Q areas. In 51 of the 74 cases (68.9%), increased V/Q areas were observed only in the lower lobes, but the others had a variety of distributions. Nineteen of the 74 patients (25.7%) had unilateral distribution of increased V/Q areas, indicating that the perfusion damage was localized to one side. Peripheral distribution of the increased V/Q areas, which was observed in 10 cases, suggested that perfusion impairment may have occurred in the peripheral portion, but these cases were excluded from the V/Q abnormal group, because the findings possibly include artifacts such as a ballooning effect.

Table 3 Abnormalities of washout time

Diseases			N-WOT*	P-WOT**	S-WOT***
SLE	without fibrosis	16	9	5	2
	with fibrosis	3	1	1	1
	with APS	15	9	4	2
RA	without fibrosis	9	3	5	1
	with fibrosis	12	3	4	5
	with APS	1		1	
PSS	without fibrosis	6	3	3	
	with fibrosis	4	6	4	4
DM-PM	without fibrosis	6	3	3	
	with fibrosis	5	3	2	
MCTD	without fibrosis	8	6	1	1
	with fibrosis	1	1		
SjS	without fibrosis	3	2	1	1
	with fibrosis	4	1	2	
	with APS	1	1		
Raynaud		3#	2	1	
PN		1	1		
Behçet		1			1
Total		109	54 (49.6%)	37 (33.9%)	18 (16.5%)

*N-WOT: normal washout time, **P-WOT: prolonged washout time, ***S-WOT: short washout time (S-WOT/Fibrosis = 18/42 = 42.9%). #All 3 patients have fibrosis



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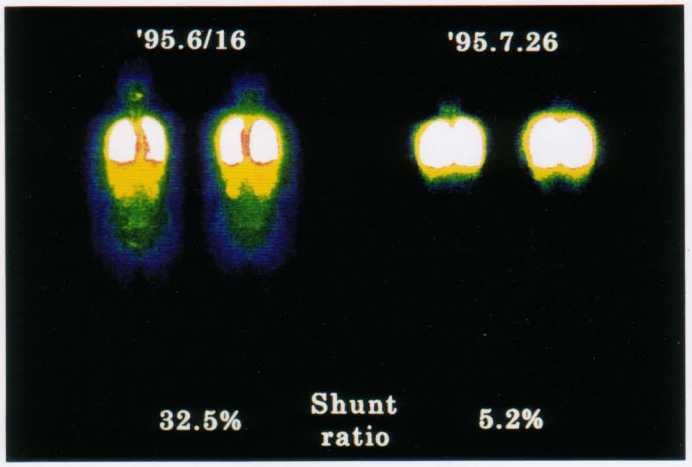

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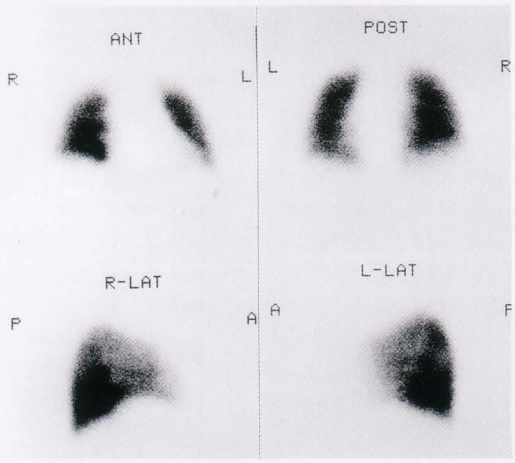


1C

Fig. 1 Case 1: A 46-year-old female with SLE. (A) HRCT of the chest shows no evidence of collagen lung. (B) Whole body scan before treatment reveals generalized uptake, especially in the kidneys and the brain, in addition to the lungs. After steroid pulse therapy, the uptake of ^{99m}Tc-MAA has localized to the lung. (C) Planar perfusion images show no focal perfusion defect or V/Q mismatch in spite of marked shunt formation.

Of the 65 patients examined by whole body scan, 8 (12.3%) had an increased shunt ratio greater than 10%, indicating formation of a PA-PV shunt secondary to peripheral vascular impairment. Thirty-eight patients (58.5%) had an equivocal shunt ratio of 7% to 10%. The remaining 19 patients (29.2%), who had shunt ratios less than 6%, were considered to have no pathological PA-PV shunt.

Wash-out time was prolonged in 37 patients (33.9%), shortened in 18 (16.5%), and normal in 54 (49.6%). The ^{133}Xe dynamic study revealed that only 18 of the 42 patients with pulmonary fibrosis (42.9%) had a short wash-out time. More than half of the patients with pulmonary fibrosis had a prolonged wash-out time, more than expected (Table 3).

Cases:

Case 1: 46-year-old female with SLE.

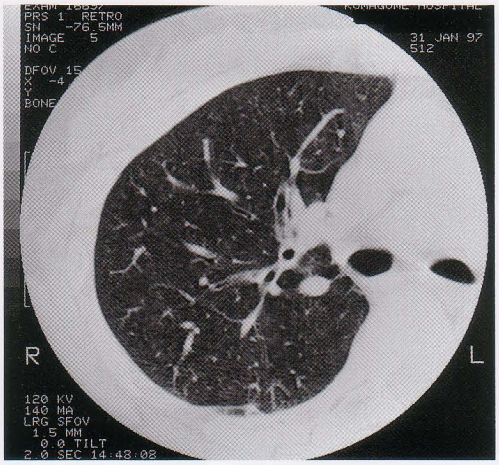
The patient was admitted because of hematuria, proteinuria, and pleural effusion. After admission, her renal function gradually deteriorated and she complained of dyspnea. Respiratory function tests showed a decreased $\%D_{LCO}$ of 56.5%, a %VC of 100%, and a $FEV_{1.0}$ of 83.2%. PaO_2 was 74% in room air.

A chest X-ray and CT scan revealed no definite evidence of collagen lung disease, but a whole body scan showed a high shunt ratio of 32.5%, suggesting the presence of a PA-PV shunt. Planar perfusion images revealed homogeneous distribution of radioactivity in both lungs without focally diminished perfusion. Steroid pulse therapy was performed, and the shunt ratio decreased to within the normal range by 6 weeks (Fig. 1). Wash-out time was within normal limits.

Case 2: 40-year-old female with SLE and APS.

The patient had been receiving treatment for SLE since 1984, and was hospitalized for sudden orthostatic dyspnea in Jan 1997. Respiratory function tests showed: %VC 47%, $FEV_{1.0}$ 87.7%, and $\%D_{LCO}$ 73.6%. PaO_2 was 87% in room air.

A chest X-ray revealed no abnormal findings. A CT scan showed only minimal fibrosis in the subpleural zone, but planar perfusion images revealed a marked decrease in perfusion in both upper lobes.



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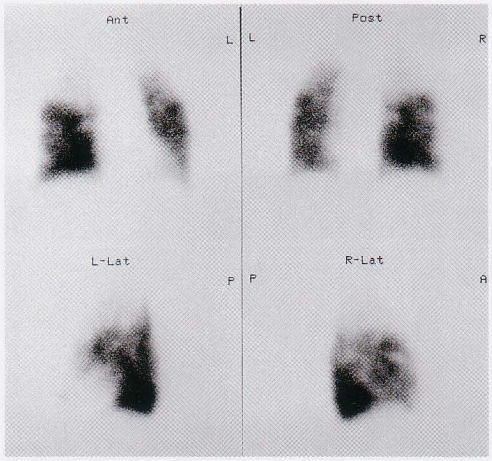
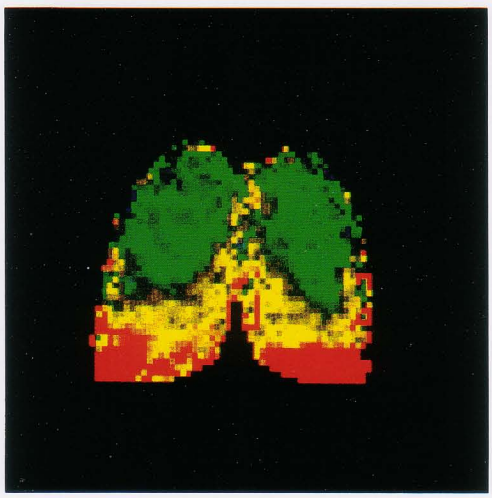


2C

Fig. 2 Case 2: A 40-year-old female with SLE and APS. (A) HRCT of the chest reveals very minimal fibrotic change in the dorsal subpleural zone. (B) Functional images of the ventilation/perfusion study in case 2. Markedly increased V/Q areas are seen in both upper lobes. (C) Planar perfusion images show decreased perfusion in both upper lobes, and multiple spotty perfusion defects are also noted in both lungs.



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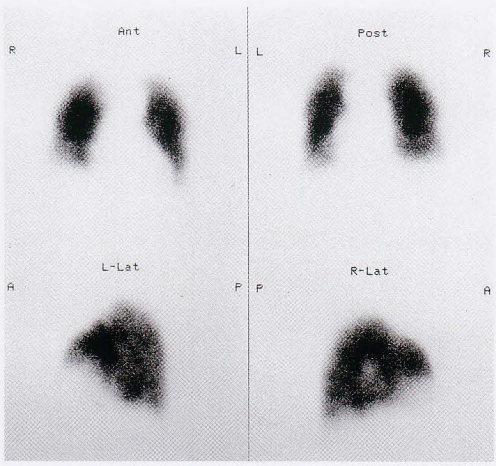

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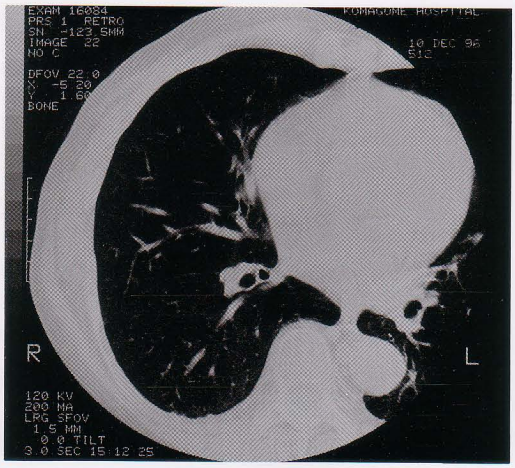

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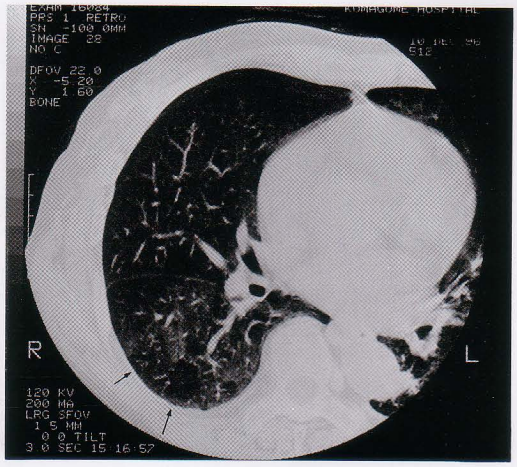
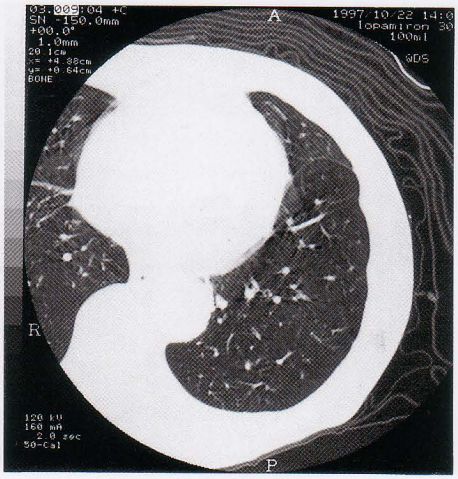


3D

Fig. 3 Case 3: A 59-year-old female with RA. (A) Functional images of the ventilation/perfusion study in case 3. Increased V/Q areas are observed in both bases. (B) Planar perfusion images show decreased perfusion in both bases. (C) HRCT appears to be normal. (D) HRCT in expiration reveals scattered air trapping in the secondary lobule (arrow), suggesting partial bronchiolitis obliterans.



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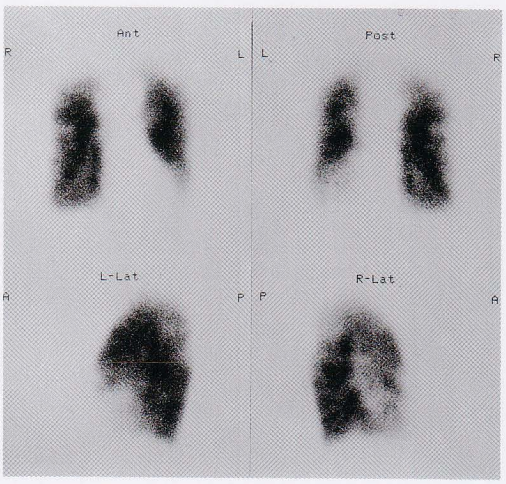

4C

Fig. 4 Case 4: A 63-year-old female with SLE and APS. (A) HRCT shows diffuse low attenuation of the lung parenchyma, especially in the left lower lobe. (B) Ventilation/perfusion study in case 4. There appears to be increased V/Q ratio in the left base and bilateral peripheral zones. Calculated washout time was prolonged (93 sec), suggesting obstructive lung disease such as bronchiolitis obliterans. (C) Planar perfusion images show an area of decreased perfusion in the left base. There also appear to be multiple small perfusion defects in both peripheral zones.

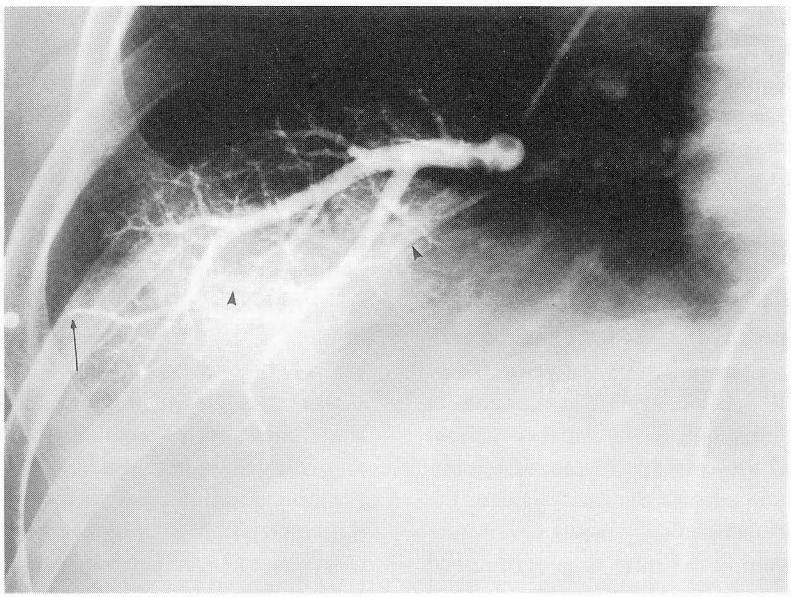

Fig. 5 Magnification wedged pulmonary arteriogram of a 60 year-old female with SjS reveals obstruction of the peripheral branches of the pulmonary artery (arrows) and early venous filling before demonstration of the capillary phase (arrowheads), suggesting PA-PV shunts.

A ventilation/perfusion image showed an increased V/Q ratio in both upper lobes, suggesting decreased pulmonary perfusion, probably due to microthromboembolism. The shunt ratio was 8.2%. Wash-out time was within normal limits (Fig. 2).

Case 3: 59-year-old female with RA.
The patient had a 9-year history of polyarthritis, and was hospitalized because of poor control of the disease. Respiratory function tests showed: %VC 105%, $FEV_{1.0}$ 70.3%, and $\%D_{LCO}$ 92.5%. Arterial blood gas analysis revealed hypoxemia with a PaO_2 of 68%. A ventilation/perfusion scan showed an increased V/Q ratio in both lower lobes. There appeared to be a minimal decrease in perfusion in the planar perfusion images in both lower lobes. Wash-out time was within normal limits. A chest X-ray and routine chest CT scan appeared normal, but a CT scan obtained during suspended full expiration showed scattered air trapping in the secondary lobules, suggesting the presence of partial bronchiolitis obliterans (Fig. 3).

Case 4: 63-year-old female with SLE and APS.
The patient had a history of low-grade fever, polyarthralgia, hematuria, erythema, and Raynaud's phenomenon since 1988, and was hospitalized because of renal failure. Respiratory function tests showed: %VC 75.3%, $FEV_{1.0}$ 69.1%, and $\%D_{LCO}$ 59.5%. A chest X-ray revealed hyperinflated lungs with no evidence of fibrosis, and a CT scan showed low attenuation of the pulmonary parenchyma, especially in the left lower lobe. The shunt ratio was 7.2%. A ventilation/perfusion scan showed an area of increased V/Q ratio in the left lower lobe.

Wash-out time was prolonged (93 sec), suggesting obstructive lung disease such as bronchiolitis obliterans. Planar perfusion images showed multiple small perfusion defects in addition to the decreased perfusion in the left lower lobe (Fig. 4).

Thermography revealed decreased blood flow in the distal portion of the extremities, and the patient was treated with steroids and an anticoagulant to prevent intravascular coagulation.

DISCUSSION

It is well known that vasculitis or pneumonitis and subsequent pulmonary fibrosis frequently occur in collagen diseases, in addition to intimal hyperplasia or intravascular microcoagulation.

In our own clinical experience, some collagen disease patients occasionally show hypoxemia or decreased D_{LCO}, even in the absence of evidence of pulmonary fibrosis on the chest X-ray. Pulmonary complications are recognized as an important prognostic factor of collagen-vascular diseases, but there have been few papers[4] evaluating collagen lung diseases by ventilation/perfusion scintigraphy.

Recently, antiphospholipid antibody syndrome (APS) has been identified as a cause of micro-thromboembolism in collagen diseases especially in SLE.[5,6] Antiphospholipid antibodies were first detected as the substances causing false serological reactions in the routine biological tests, and after a while had been recognized as those affecting a blood coagulation mechanism. Although there are many kinds of antibodies and antigens relating to APS,

anticardiolipin antibody and lupus anticoagulant are representative and usable antibodies in clinical cases in Japan. There are no differences in the number of patients with an increased V/Q ratio among the three groups shown in Table 1. This may mean that the presence of APS does not necessarily result in perfusion impairment in all cases.

Early detection and adequate treatment of vasculitis or intravascular coagulation occurring in collagen lung diseases might improve the long term survival of patients.[7]

The fact that increased V/Q areas were observed in many patients in our series indicates the presence of perfusion impairment at the time of the examination. In view of the fact that almost half of the patients without evidence of fibrosis had V/Q abnormality, perfusion impairment appears to occur even in the early stage of the diseases. Long-term follow up of the patients who have a V/Q abnormality detected in the early stage will reveal subsequent progression to pulmonary fibrosis.

The increased V/Q areas appear to often be localized or heterogeneous in distribution, as shown in the V/Q study. The location and grade of these areas sometimes changed in the course of the disease, which may represent improvement or deterioration of the disease.

PA-PV shunt tracts, which minimally dilate in the physiological state, may dilate enough to allow us to detect them by ^{99m}Tc-MAA scintigraphy in the state of diffusely and severely impaired capillary blood flow to prevent acute failure of the right ventricle, resulting in severe hypoxemia without any radiographic changes in the chest X-rays as shown in case 1. Inhalation studies with 100% oxygen are a standard method of determining the shunt ratio, but this method is physiological and comprises all shunt ratios, including intracardiac shunts.[8] Magnification wedged pulmonary arteriography is also capable of visualizing PA-PV shunts on X-ray films (Fig. 5), but shunt ratio data cannot be obtained.[9,10] In the preliminary study in this series, the authors attempted to carry out pulmonary arteriography to obtain correct data on pulmonary arterial pressure as well as to detect vascular abnormalities, but this technique was very invasive and unacceptable to many patients.

Gallium-67 scans are sensitive enough to evaluate the activity of pneumonitis.[11] Pulmonary clearance of ^{99m}Tc-DTPA is the most sensitive method of evaluating epithelial impairment of the peripheral airways and alveoli,[12] but these methods are incapable of demonstrating directly whether these abnormal findings are caused by vasculitis or microthromboembolism.

After some clinical trials, we reached the conclusion that the ventilation/perfusion scan was the best examination method for our clinical purposes.

Whole body scans after a perfusion study with ^{99m}Tc-MAA appear to be the best method of demonstrating PA-PV shunts, but particle size in the ^{99m}Tc-MAA preparation is 20–60 μm, and therefore PA-PV shunts smaller than this might not be calculated in the shunt ratio. Normal physiological shunts are generally observed in the ratio of 3–6%,[3] and for this reason the authors adopted shunt ratios over 10% as the abnormal range. Shunt ratios between 7% and 10% were considered equivocal. Whether the level adopted as abnormal in our study is reasonable may be debatable. Although there have been reports on the use of ^{99m}Tc-MAA whole-body scans to detect intrapulmonary right-to-left shunts in patients with pulmonary arteriovenous malformations[13] and hepatopulmonary syndrome,[14,15] no papers have ever been published on collagen lung diseases.

According to the literature, collagen disease patients sometimes develop small airway diseases, such as bronchiolitis obliterans, in addition to vascular diseases.[16] Prolonged and normal wash-out time in patients with pulmonary fibrosis might represent the presence of an obstructive disease superimposed on the fibrosis, because patients with pulmonary fibrosis usually have short wash-out time. As shown in case 3, CT scans in expiration are a convenient method of demonstrating bronchiolitis obliterans secondary to collagen disease.

Henriksen et al.[17] examined 13 healthy subjects by using ^{133}Xe gas and determined the average mean transit time to be 37 ± 17 sec. Although the normal range adopted in our study appears to be somewhat longer than in Henriksen's data, both are actually concordant. ^{133}Xe dynamic studies, as well as V/Q images, are useful in evaluating small airway disease in collagen lung disorders.

The authors did not mention the relationship between the V/Q ratio and respiratory function in the results of this study, because it appeared to be very complicated. In the preliminary study, there was no correlation by linear regression analysis between the shunt ratio and PaO_2 ($r = 0.41$, $n = 15$) as well as D_{LCO} ($r = -0.075$, $n = 31$). Many patients with normal pulmonary function showed signs of V/Q abnormality, whereas some of the patients with abnormal pulmonary function had results matching those of the V/Q study. Ordinarily, almost pulmonary diseases with alveolar hypoxia reduce pulmonary perfusion concomitant with a disturbance of ventilation, resulting in matched V/Q.[18] Our data indicate that the phenomenon of an increased V/Q ratio is not related directly to ventilation, or to be intricate in mechanism.

On the other hand, the wash-out time appeared to be closely related to pulmonary function, especially to a forced expiratory volume of 1 sec ($FEV_{1.0}$). Further analysis and research should be carried out to solve these problems.

CONCLUSION

In our study of 109 patients with various collagen diseases, ventilation/perfusion scans detected not only perfusion impairment but small airway obstruction, even in

the early stage of the disease. This method is a very sensitive and useful tool for the evaluation of collagen diseases, and may contribute to diagnosis and treatment.

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